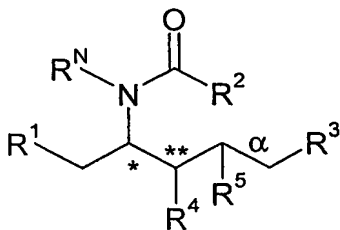


CLAIMS

1. A pharmaceutical formulation comprising:

(i) a drug; and

5 (ii) a short-chain sphingolipid selected from compounds of the following formula:



wherein:

R¹ is independently:

an O-linked saccharide group; or

10 an O-linked polyhydric alcohol group;

or:

R¹ is independently:

an O-linked (optionally N-(C₁₋₄alkyl)-substituted amino)-C₁₋₆alkyl-phosphate group; or

15 an O-linked (polyhydric alcohol-substituted)-C₁₋₆alkyl-phosphate group;

R² is independently C₃₋₉alkyl,

and is independently unsubstituted or substituted;

R³ is independently C₇₋₁₉alkyl,

20 and is independently unsubstituted or substituted;

R⁴ is independently -H, -OH, or -O-C₁₋₄alkyl;

R^N is independently -H or C₁₋₄alkyl;

the bond marked with an alpha (α) is independently a single bond or a double bond;

25 if the bond marked with an alpha (α) is a double bond, then R⁵ is -H;

if the bond marked with an alpha (α) is a single bond, then R⁵ is -H or -OH;

the carbon atom marked (*) is independently in an R-configuration or an

S-configuration;

the carbon atom marked (**) is independently in an R-configuration or an

30 S-configuration;

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and pharmaceutically acceptable salts, solvates, esters, ethers, chemically protected forms thereof.

* * *

5

2. A pharmaceutical formulation according to claim 1, wherein said drug is an amphiphilic drug.

10

3. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anthracycline.

4. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anti-proliferative anthracycline

15

5. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anti-cancer anthracycline.

20

6. A pharmaceutical formulation according to claim 1, wherein said drug is selected from: doxorubicin, idarubicin, epirubicin, aclarubicin, mitrozantrone, and daunorubicin, and salts thereof.

7. A pharmaceutical formulation according to claim 1, wherein said drug is doxorubicin or doxorubicin hydrochloride.

25

8. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an alkaloid.

9. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anti-proliferative alkaloid

30

10. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anti-cancer alkaloid.

35

11. A pharmaceutical formulation according to claim 1, wherein said drug is selected from: topotecan and camptothecin.

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* * *

12. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R² is independently linear.

13. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R² is independently saturated or partially unsaturated.

14. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R² is independently linear; and saturated or partially unsaturated.

15. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R² is independently linear; and has from 0 to 3 carbon-carbon double bonds.

16. A pharmaceutical formulation according to any one of claim 1 to 15, wherein R² is independently unsubstituted or substituted with from 1 to 3 substituents selected from C₁₋₄alkyl, -OH, C₁₋₄alkoxy, -C(=O)OH, and -C(=O)O-C₁₋₄alkyl.

17. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R² is independently -(CH₂)_nCH₃, wherein n is an integer from 2 to 8.

18. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R² is independently -(CH₂)_nCH₃, wherein n is an integer from 4 to 8.

19. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R² is independently -(CH₂)_nCH₃, wherein n is an integer from 6 to 8.

20. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R² is independently -(CH₂)₆CH₃.

* * *

21. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the bond marked alpha is independently a double bond and R⁵ is -H.

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22. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the bond marked alpha is independently a single bond; and R⁵ is -H or -OH.
23. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the bond marked alpha is independently -CH₂-CH₂-.
24. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the bond marked alpha is independently -CHOH-CH₂-.

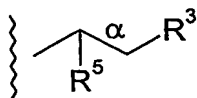
* * *

25. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R³ is independently linear.
26. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R³ is independently saturated or partially unsaturated.
27. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R³ is independently linear; and saturated or partially unsaturated.
28. A pharmaceutical formulation according to any one of claims 1 to 27, wherein R³ is independently unsubstituted or substituted with from 1 to 3 substituents selected from C₁₋₄alkyl, -OH, C₁₋₄alkoxy.
29. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R³ is independently -(CH₂)_nCH₃, wherein n is an integer from 8 to 16.
30. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R³ is independently -(CH₂)₁₂CH₃.

* * *

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31. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the moiety:



is selected from the following:

- 5 -(CH₂)₈-CH₃ (from caproic acid) ("C10");
 -(CH₂)₁₀-CH₃ (from lauric acid) ("C12");
 -(CH₂)₁₂-CH₃ (from myristic acid) ("C14");
 -(CH₂)₁₄-CH₃ (from palmitic acid) ("C16");
 -(CH₂)₇-CH=CH-(CH₂)₅-CH₃ (from palmitoleic acid) ("C16");
 10 -(CH₂)₁₆-CH₃ (from stearic acid) ("C18");
 -(CH₂)₇-CH=CH-(CH₂)₇-CH₃ (from oleic acid) ("C18");
 -(CH₂)₉-CH=CH-(CH₂)₆-CH₃ (from vaccenic acid) ("C18");
 -(CH₂)₇-[CH=CH-CH₂]₂-(CH₂)₃-CH₃ (from linoleic acid) ("C18");
 -(CH₂)₇-[CH=CH-CH₂]₃-CH₃ (from (9,12,15-linoleic acid) ("C18");
 15 -(CH₂)₄-[CH=CH-CH₂]₃-(CH₂)₃-CH₃ (from (6,9,12-linoleic acid) ("C18");
 -(CH₂)₇-[CH=CH]₃-(CH₂)₃-CH₃ (from eleostearic acid) ("C18");
 -(CH₂)₁₈-CH₃ (from arachidic acid) ("C20");
 -(CH₂)₆-[CH=CH-CH₂]₂-(CH₂)₆-CH₃ ("C20");
 -(CH₂)₃-[CH=CH-CH₂]₃-(CH₂)₆-CH₃ ("C20");
 20 -(CH₂)₃-[CH=CH-CH₂]₄-(CH₂)₃-CH₃ ("C20");
 -(CH₂)₂₀-CH₃ (from behenoic acid) ("C22");
 analogues wherein the left-most -(CH₂)₂- is replaced with -CH=CH-; and
 analogues wherein the left-most -(CH₂)- is replaced with -CH(OH)-.

25

* * *

32. A pharmaceutical formulation according to any one of claims 1 to 31, wherein R⁴ is independently -H, -OH, -OMe, -OEt, -O(iPr), -O(nPr), -O(nBu), -O(iBu), -O(sBu), or -O(tBu).
- 30 33. A pharmaceutical formulation according to any one of claims 1 to 31, wherein R⁴ is independently -H, -OH, or -OMe.

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34. A pharmaceutical formulation according to any one of claims 1 to 31, wherein R⁴ is independently -H or -OH.

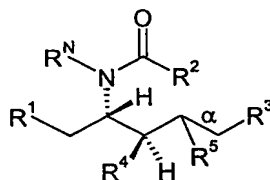
35. A pharmaceutical formulation according to any one of claims 1 to 31, wherein R⁴ is independently -OH.

* * *

36. A pharmaceutical formulation according to any one of claims 1 to 35, wherein R^N is independently -H, -Me, or -Et.

* * *

37. A pharmaceutical formulation according to any one of claims 1 to 36, wherein the carbon atoms marked (*) and (**) have a configuration as shown in the following formula:



38. A pharmaceutical formulation according to any one of claims 1 to 36, wherein the carbon atoms marked (*) and (**) have the same configuration as in naturally occurring sphingosine.

* * *

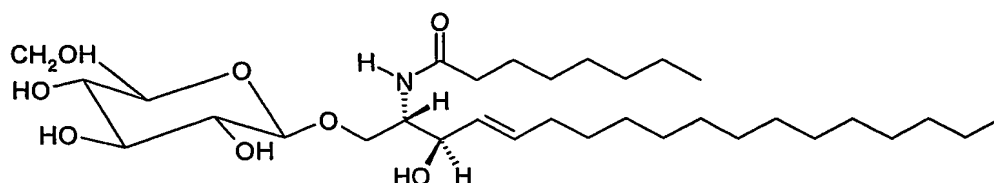
39. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently:

an O-linked saccharide group; or
an O-linked polyhydric alcohol group.

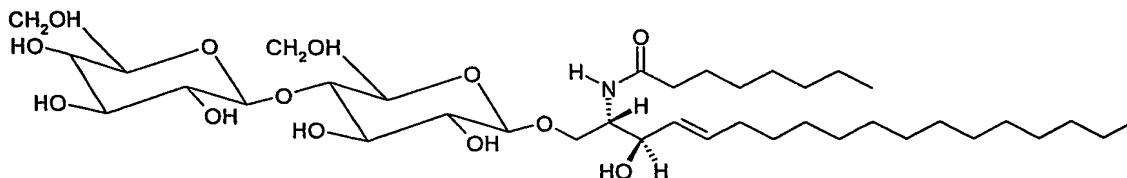
40. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently an O-linked saccharide group.

41. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently an O-linked mono-, di-, or tri-saccharide group.
- 5 42. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently an O-linked mono- or di-saccharide group.
43. A pharmaceutical formulation according to any one of claims 1 to 42, wherein R¹ is formed from pentose and/or hexose groups.
- 10 44. A pharmaceutical formulation according to any one of claims 1 to 42, wherein R¹ is formed from a group or groups selected from:
arabinose, lyxose, ribose, or xylose;
allose, altrose, glucose, mannose, gulose, idose, galactose, or talose;
and derivatives thereof.
- 15 45. A pharmaceutical formulation according to any one of claims 1 to 42, wherein R¹ is independently an O-linked mono-, di-, or tri-saccharide group derived from:
arabinose, lyxose, ribose, or xylose;
allose, altrose, glucose, mannose, gulose, idose, galactose, or talose;
20 sucrose, maltose, lactose, cellobiose, or galabiose;
globotriaose, isoglobotriaose, mucotriaose, lactotriaose, neolactotriaose
gangliotriaose, galatriaose, mollutriaose, or antrotriaose;
or a derivative thereof.
- 25 46. A pharmaceutical formulation according to claim 44 or 45, wherein said saccharide group derivatives are selected from deoxy, di-deoxy, di-deoxy-di-dehydro, methoxy (-OMe), acetoxy (-OC(=O)Me), carboxylic acid (-C(=O)OH), sulfuric acid (-OSO₃H), amino-deoxy (e.g., -NH₂), N-acetyl-amino-deoxy (e.g., -NHC(=O)Me), or N-sulfo-amino-deoxy (e.g., -NHS(O)₂OH) derivatives.
- 30

47. A pharmaceutical formulation according to claim 1, wherein said short-chain sphingolipid has the following formula (C₈-GlcCer):



- 5 48. A pharmaceutical formulation according to claim 1, wherein said short-chain sphingolipid has the following formula:



- 10 49. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently an O-linked polyhydric alcohol group.

50. A pharmaceutical formulation according to claim 49, wherein R¹ is formed from groups selected from: ethanediol (glycol), propanediol, butanediol, glycerol, and erythritol.

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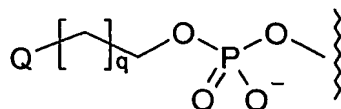
* * *

51. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently:
 20 an O-linked (optionally N-(C₁₋₄alkyl)-substituted amino)-C₁₋₆alkyl-phosphate group; or
 an O-linked (polyhydric alcohol-substituted)-C₁₋₆alkyl-phosphate group.

52. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently an O-linked (optionally N-(C₁₋₄alkyl)-substituted amino)-C₁₋₆alkyl-phosphate group.

25

53. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently:

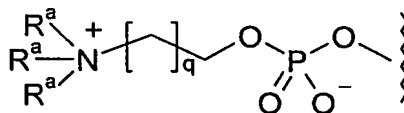


wherein:

- 5 q is independently an integer from 0 to 5;
 Q is independently: -NH₂, -NHR^a, -NR^a₂, or -NR^a₃⁺; or:
 Q is independently a polyhydric alcohol group, linked via an oxygen atom;
 each R^a is independently linear or branched saturated C₁₋₄alkyl.

- 10 54. A pharmaceutical formulation according to claim 53, wherein Q is independently:
 -NH₂, -NHR^a, -NR^a₂, or -NR^a₃⁺.

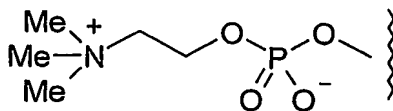
55. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently:



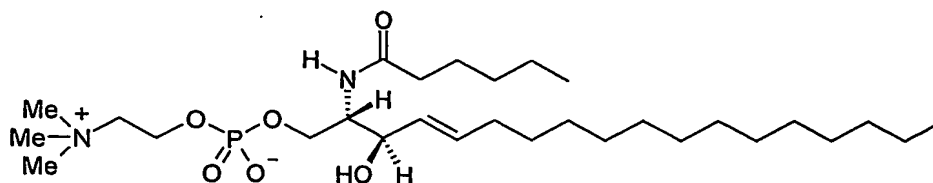
wherein:

- q is independently an integer from 0 to 5; and
 each R^a is independently a C₁₋₄alkyl group.

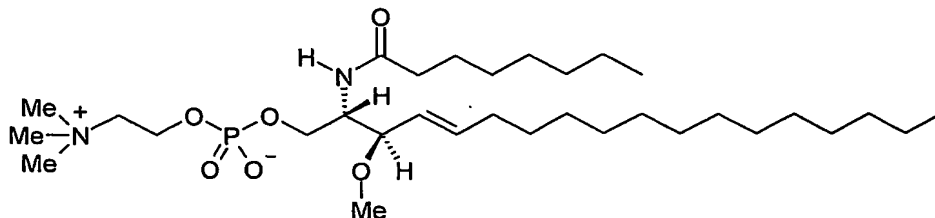
- 20 56. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R¹ is independently:



- 25 57. A pharmaceutical formulation according to claim 1, wherein said short-chain sphingolipid has the following formula ("C₆-SM"):



58. A pharmaceutical formulation according to claim 1, wherein said short-chain sphingolipid has the following formula ("3-O-methyl-C₈-SM"):



5

59. A pharmaceutical formulation according to claim 53, wherein Q is independently a polyhydric alcohol group, linked via an oxygen atom.
60. A pharmaceutical formulation according to claim 59, wherein Q is formed from a group selected from: ethanediol (glycol), propanediol, butanediol, glycerol, and erythritol.

10

* * *

61. A pharmaceutical formulation according to any one of claims 1 to 60, wherein said pharmaceutical formulation additionally comprises one or more other pharmaceutically acceptable ingredients selected from pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, and surfactants.
62. A pharmaceutical formulation according to any one of claims 1 to 61, wherein said pharmaceutical formulation is suitable for parenteral administration.

20

* * *

63. A pharmaceutical formulation according to any one of claims 1 to 62, wherein the pharmaceutical formulation is a liposomal pharmaceutical formulation.

25

* * *

30

- 5
64. A liposomal pharmaceutical formulation according to claim 63, wherein the liposomes of the liposomal pharmaceutical formulation are prepared using a mixture of lipids comprising, at least, vesicle-forming lipids and said short-chain sphingolipid.
65. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises phospholipids and said short-chain sphingolipid.
- 10 66. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises phospholipids, cholesterol, and said short-chain sphingolipid.
- 15 67. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises phosphatidylcholines, cholesterol, and said short-chain sphingolipid.
- 20 68. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises fully hydrogenated soy phosphatidylcholine (HSPC), cholesterol, and said short-chain sphingolipid.
- 25 69. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises dipalmitoyl-phosphatidylcholine (DPPC), cholesterol, and said short-chain sphingolipid.
- 30 70. A liposomal pharmaceutical formulation according to any one of claims 64 to 69, wherein said mixture of lipids additionally comprises a vesicle-forming lipid which is derivatized with a polymer chain.
71. A liposomal pharmaceutical formulation according to any one of claims 64 to 69, wherein said mixture of lipids additionally comprises a phosphatidylethanolamine (PE) which is derivatized with polyethyleneglycol (PEG).
- 35 72. A liposomal pharmaceutical formulation according to any one of claims 64 to 69, wherein said mixture of lipids additionally comprises N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG2000-DSPE).

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* * *

5 73. A liposomal pharmaceutical formulation according to any one of claims 64 to 72, wherein the amount of short-chain sphingolipid is 1-25 mol%.

74. A liposomal pharmaceutical formulation according to any one of claims 64 to 73, wherein the amount of cholesterol, if present, is 20-50 mol%.

10 75. A liposomal pharmaceutical formulation according to any one of claims 64 to 74, wherein the amount of phospholipid, excluding phospholipid which is derivatized with a polymer chain, if present, is 45-70 mol%.

15 76. A liposomal pharmaceutical formulation according to any one of claims 64 to 75, wherein the amount of vesicle-forming lipid which is derivatized with a polymer chain, if present, is 1-15 mol%.

20 77. A liposomal pharmaceutical formulation according to any one of claims 64 to 76, wherein said liposomes of said liposomal pharmaceutical formulation comprise 0.05-0.50 μ mol drug per μ mol phospholipid.

* * *

25 78. A liposomal pharmaceutical formulation according to any one of claims 64 to 77, wherein said liposomes additionally comprise other pharmaceutically acceptable ingredients selected from: ammonium sulfate, histidine, hydrochloric acid and/or sodium hydroxide, sucrose, and water-for-injection.

* * *

30 79. A liposomal pharmaceutical formulation according to any one of claims 64 to 78, wherein said liposomes have a mean diameter of 50 to 150 nm.

* * *

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80. Caelyx® or Doxil® liposomes post-inserted with a short-chain sphingolipid as defined in any one of claims 1 and 12 to 60.

* * *

5

81. A pharmaceutical formulation according to any one of claims 1 to 80, for use in a method of treatment of the human or animal body by therapy.

10

82. Use of:

(i) a drug, as defined in any one of claims 1 to 11; and
(ii) a short-chain sphingolipid, as defined in any one of claims 1 and 12 to 60;
in the manufacture of a medicament for the treatment of a proliferative condition in a human or animal patient.

15

83. Use according to claim 82, wherein said proliferative condition is cancer.

84. Use according to claim 82, wherein the drug is doxorubicin or a salt thereof; and the proliferative condition is a proliferative condition that is treated by doxorubicin or a salt thereof.

20

85. A method of treating a proliferative condition comprising administering to a patient in need of treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 80.

25

86. A method according to claim 85, wherein said proliferative condition is cancer.

87. Use according to claim 85, wherein the drug is doxorubicin or a salt thereof; and the proliferative condition is a proliferative condition that is treated by doxorubicin or a salt thereof.

30

88. A method of making a pharmaceutical formulation according to any one of claims 1 to 79, comprising the step of admixing said drug and said short-chain sphingolipid.

89. A method of making a liposomal pharmaceutical formulation according to any one of claims 63 to 80, comprising the steps of:

(a) forming a lipid mixture comprising, at least, vesicle-forming lipids and said short-chain sphingolipid;

5 (b) forming liposomes from said lipid mixture; and

(c) adding said drug to the liposomes formed in (b);
thereby forming liposome-entrapped drug.

90. A method of making a liposomal pharmaceutical formulation according to any one of claims 63 to 79, comprising the steps of:

10 (a) forming a lipid mixture comprising, at least, vesicle-forming lipids and said short-chain sphingolipid;

(b) adding said drug to said lipid mixture;

(c) forming liposomes from the mixture formed in (b);
15 thereby forming liposome-entrapped drug.

* * *

91. A method of increasing the bioavailability and/or cellular uptake of a drug, as
20 defined in any one of claims 1 to 11, which method includes the step of
co-administering said drug with a short-chain sphingolipid, as defined in any one
of claims 1 and 12 to 60.